

## CLAIM AMENDMENTS

1. (Currently amended) A method for reducing cell aggregation during [~~Process for the culturing of cells by~~] continuous perfusion culturing of a cell culture comprising cell culture medium and animal cells, wherein cell culture medium is added to the cell culture, the cell culture is circulated over a filter module comprising hollow fibers in an alternating tangential flow resulting in an outflow of liquid having a lower animal cell density than the cell culture~~], and the flow within the filter module is an alternating tangential flow]~~, wherein no more than 5% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing, and wherein the culturing is continued until animal cells are present in the cell culture at a density of at least  $80 \times 10^6$  animal cells/ml.

2. (Currently amended) The method of [~~Process according to~~] claim 1, wherein the cell culture medium is added at a perfusion rate calculated according to Formula 1:

Perfusion rate=Specific perfusion rate (SPR)\*total cell culture volume\*viable cell density

wherein the perfusion rate is expressed in liters per day, [~~wherein the SPR is the specific perfusion rate, i.e. the rate in which the cell culture medium is fed to the cell culture expressed as the volume of medium added per viable cell per time unit]~~ and wherein the viable cell density is the number of viable cells per unit of volume.

3. (Currently amended) The method of [~~Process according to~~] claim 2, wherein the SPR is between 0.01 and 0.3 nL/animal cell/day.

4. (Currently amended) The method of [~~Process according to~~] claim 1, wherein biomass is removed at least once from the cell culture and additional cell culture medium is added to the cell culture.

5. (Currently amended) The method of [~~Process according to~~] claim 4, wherein the biomass removal is started just before or just after the cells have reached a steady state.

6. (Currently amended)      The method of ~~[Process according to]~~ claim 4, wherein a volume of biomass is removed of between 2 and 40% of the total volume of the cell culture per day.
7. (Currently amended)      The method of ~~[Process according to]~~ claim 1, wherein the alternating tangential flow is achieved using one pump to circulate the cell culture within ~~over~~ a) the filter module comprising hollow fibers and using another pump to remove the liquid having a lower cell density than the cell culture prior to the filter separation.
8. (Currently amended)      The method of ~~[Process according to]~~ claim 1, wherein the animal cells are cultured to a ~~viable cell density of at least  $80 \times 10^6$  cells per ml and a~~ cell viability of at least 90%.
9. (Currently amended)      The method of ~~[Process according to]~~ claim 1, wherein no more than 4% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing ~~[the aggregates of at least 5 cells comprise at the most 5% of the total amount of cells]~~.
10. (Canceled)      ~~Process according to claim 1, wherein the cells are animal cells, preferably mammalian cells, or yeast cells.~~
11. (Currently amended)      The method of ~~[Process according to]~~ claim 10, wherein the cells are mammalian cells.
12. (Currently amended)      The method of ~~[Process according to]~~ claim 11, wherein the mammalian cells are human ~~[PER-C6@]~~ cells.
13. (Currently amended)      The method of ~~[Process according to]~~ claim 1, wherein the cells produce a biological substance.
14. (Currently amended)      The method of ~~[Process according to]~~ claim 13, wherein the

biological substance is a ~~[therapeutic or diagnostic] protein [such as a monoclonal antibody, a growth factor or a peptide hormone, an enzyme,] or a polynucleotide [such as a viral vector used in gene therapy, or a vaccine, preferably a monoclonal antibody].~~

15. (Currently amended)      The method of ~~[Process according to]~~ claim 13, wherein the biological substance is further purified in downstream processing.